REMARKS

This is in response to the non-Final Office action (Unnumbered Paper) mailed 28 May 2008.

Claims 1 through 4 and 6 through 18 are pending and under the Examiner's consideration.

Claims 4 and 7 have been amended by this Amendment.

No new matter has been added.

I. Sequence Compliance

The specification has been amended. There is no specified four or more amino acid sequence which are embraced by CFR 37 CFR §§ 1.821-1.825.

II. Claim Rejections – 35 USC § 112

Claims 1-4 and 6-18 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The examiner's analysis is based on misunderstanding of the metabolic syndrome and the present invention for the following reasons.

1. First, the examiner's reasoning related to 35 U.S.C. §112 is inconsistent with the examiner's reasoning related to 35 U.S.C. §§ 102 and 103. The examiner argued that the specification does not give sufficient information to one skilled in the art to make use of the invention, requiring too much experimentation and, at the same time, the examiner argued that the invention is obvious and/or anticipated by an older Gottlieb patent and that of Chibret.

2. Second, the examiner did not carefully consider the specification.

The specification as filed provided a nexus between chronic inflammation and the metabolic syndrome or metabolic disturbances, and supported that the claimed pharmaceutical compositions can treat them.

It should be noted that, as pointed out by the examiner, the metabolic syndrome is drawn to a constellation of symptoms.

The specification expressly discloses that:

"[0005] The distribution of fat characteristic of the Metabolic Syndrome (Syndrome X) (a precursor to a form of Type II Diabetes) resembles the lipodystrophy seen in longer term HIV Disease survivors, and which is also associated with insulin resistance. There is currently a debate as to whether the cause of lipodystrophy and abnormal glucose tolerance in HIV survivors is due to treatment with protease inhibitors, or to long-term survival with HIV infection. There is clearly continual antigenic stimulation in this situation. Chronic antigenic stimulation results in inflammation which, in turn, can result in abnormal immune function, cardiovascular disease, and other sequelae.

[0006] Earlier studies had described that Type II diabetes had a very strong familial (dominant) inheritance pattern (GOTTLIEB AND ROOT, DIABETES 17:693-704, 1968). Current Type II diabetes, associated with the Metabolic Syndrome, has not been reported to have such a familial association (SINHA, ET AL., N. ENGL. J. MED. 346:802-810, 2002).

[0007] Studies have shown an increase in coronary heart disease mortality in association with air pollution and increased diabetes mellitus in association with release of dioxins (for example, HENRIKSEN, GL, EPIDEMIOLOGY 8:252-8(1097)). C-Reactive Protein levels have been elevated in these studies. (Elevated C-Reactive Protein is a marker for an inflammatory response.) The frequency of obesity has been increasing markedly in all populations.

[0008] Therefore, chronic antigenic stimulation, whether by infection or environmental pollutants can overwhelm the innate immune system's ability to control (remove) these substances leading to uncontrolled inflammation, failure of insulin to affect liver and muscle enzymes to control blood glucose, leading to impaired glucose tolerance, hyperinsulinemia, insulin resistance, dyslipidemia, elevated triglycerides, and i.e. the Metabolic Syndrome."

That is, in the specification, the inventors of the present application first discloses that chronic antigenic stimulation may result in the Metabolic syndrome with data of the prior art.

In addition to the data in the prior art references, the specification also includes Tables 1 and 2 to support the inventor's theory. More particularly, the specification expressly states that:

[0056] The Metabolic Syndrome, or Syndrome "X", is a recently described illness which is characterized by obesity, insulin resistance, hypertension, dyslipidemia, decreased serum HDL-L, elevated serum triglycerides, impaired glucose tolerance, polycystic ovary syndrome, increased acute phase proteins, including C-Reactive Protein and fibrinogen, and leads to diabetes mellitus, coronary artery disease, and cancer. Coronary Heart Disease and Diabetes Mellitus have been reported to be increased in populations chronically exposed to air pollution and to dioxins. People who are long-term survivors with AIDS develop a lipodystrophy with features very similar to the Metabolic Syndrome. Both of these populations are subject to chronic antigenic stimulation.

[0057] There are data from a clinical trial in patients with HIV Disease, using the leukocyte-derived immunoregulator which has YG and YGG as the active components (GOTTLIEB, MS. ANNALS OF INTERNAL MEDICINE. 115:84 (1991)), which were not examined with regard to evaluation of the immunoregulator, that are useful with regard to the current thinking concerning the Metabolic Syndrome. Re-examination of some of the toxicity evaluation data collected during the clinical trial showed that during the course of the trial, mean serum glucose increased in those who received placebo ($p<0.015$) and became significantly higher than in those treated with the immunoregulator ($p<0.043$), which either declined if all subjects were included or rose slightly if only those subjects with normal values at baseline were included (Table 1).

[0058] Similarly, blood platelets which contribute to the coagulopathy associated with the Metabolic Syndrome, were "reduced" in treated patients and significantly increased in those receiving placebo ($p=0.038$). The between group difference was significant ($p=0.032$) (Table 1)."

"[0060] These findings support an hypothesis that uncontrolled and chronic antigenic stimulation due to infection (HIV is present in many tissues and cells once infection has occurred) or environmental pollutants, and the relative immunologic deficiency and failure to effectively remove such foreign material due to an overwhelming antigen and/or reduced immune function load may be contribute to the metabolic syndrome and insulin resistance which is a result of interference with insulin activity and the activity of enzymes related to glucose metabolism. Correction of such immune deficiency or dysregulation with the unique immunoregulators described herein appears to correct key components of the metabolic syndrome and lipoatrophic diabetes mellitus associated with HIV Disease. Based on these findings, it is possible, then to treat patients who have or who are at risk for the Metabolic Syndrome with one or more of the immunoregulators described herein, and thus to prevent the Diabetes Mellitus, Coronary Heart Disease, Cancer, and other outcomes associated with the Metabolic Syndrome which is seen in increasing frequency worldwide, and more so in areas of increased pollution, and in populations with high prevalence of and at high risk for chronic infections, e.g. tuberculosis and malaria, by improving the individual's immune function."

In view of these disclosures and evidence (which includes the cited references in the specification), the disclosure provides a nexus between chronic inflammation and the metabolic syndrome or metabolic disturbance.

The examiner did not consider the above disclosure and evidence, and did improperly argue that essentially all of the work required to ultimately develop a treatment method (including clinical trials) has been left for others.

It should be noted that "The evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art." (MPEP §2164.05)

In view of the specification and the cited references, the evidence therein is at least convincing to one skilled in the art. The examiner's reasoning seems to require the evidence to be conclusive. (It should be also noted that, since, as pointed out by the examiner, the metabolic syndrome is drawn to a constellation of symptoms, there is no conclusive evidence for the metabolic syndrome.)

Since the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing, withdrawal of the rejection is respectfully requested.

3. The examiner's attention is also invited to consider *In re Strahilevits*, 668 F.2d 1229, 212 USPQ 561 (CCPA 1982).

In *In re Strahilevitz,* applicants sought to broadly claim a method and devices for removing heptens, antigens, and antibodies from blood. Applicants had not disclosed even a single operative embodiment. The court held that "We recognize that working examples are desirable in complex technologies and that detailed examples can satisfy the statutory enablement requirement. Indeed, the inclusion of such examples here might well have avoided a lengthy and, no doubt, expensive appeal. Nevertheless, ... *examples are not required to satisfy section 112, first paragraph*" And that "Although the invention is applicable to a large variety of haptens and antigens, the examiner offered no reason why these different compounds would require different techniques or process parameters." *In re Strahilevits*, 212 USPQ 561, 563 (CCPA 1982)

Like *In re Strahilevitz*, the examiner offered no clear reason why the examiner doubts that the effect mechanism and/or nexus of the claimed methods. The examiner's reasoning is at most that the art is unpredictable. As stated above, in view of level of skill, state of the art and the information in the specification, one skilled in the art would expect the claimed methods could be used in that manner without undue experimentation.

Further, the specification includes not only a working example but also prophetic examples. Even if the prophetic examples are not actual evidence, these prophetic examples supports the enablement by showing how to apply the claimed method to other pathogens.

Withdrawal of the rejection is respectfully requested.

III. Claim Rejections – 35 USC §§ 102, 103

Claims 1, 10-16 and 18 stand rejected under 35 U.S.C. 102(b) as being anticipated by Gottlieb (US 4,468,379, cited in the IDS of 11/07) as evidenced by Chibret (US 5,000,936).

Claims 1-18 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gottlieb '379, in view of Chibret '936 relied upon as in the anticipation rejection, and Hundal *et al.* (The Journal of Clinical Investigation May 2002, cited in the IDS of 11/07).

1. Gottlieb '379 in view of Chibret '936 and Hundal *et al.* do not teach the use of the claimed pharmaceutical composition for the claimed methods.

The examiner argued that Gottlieb teaches the use of purified leukocyte dialysate subfraction has anti-inflammatory properties, and teaches treating suppression and prevention of contact dermatitis.

(1) Gottlieb '379 teaches a group of substances derived from human leukocytes, but regarding contact dermatitis, what Gottlieb '379 teaches is the use of S-suppressor for suppression of contact dermatitis and the use of L-suppressor for prevention of contact dermatitis. (See Examples 12 and 13 in Gottlieb '379. See also col. 13, lines 50-54: "reduced inflammation is observed at HP-3 treated sites, due to the presence of suppressor activity, which appears to predominate over the activity of any amplifiers in this fraction.")

Neither the L-Suppressor nor the S-Suppressor is the same as the immunomodulator or immunoamplifier fraction he also describes or the claimed composition. (See col. 24 in Gottlieb '379 and the definitions in the specification of the instant application at page 11, line 6 to page 13, line 11 for the cited pharmaceutical compositions.)

Further, Gottlieb '379 teaches that the YG and YGG materials which are the subject of the instant application are found in a fraction known as Beta-1.0 which is entirely different from the L-and S-Suppressors. Further, it would not have occurred either at the time of the invention described in the '379 patent or at the time the present invention was made that an immunoamplifier would control an inflammatory process. (As stated above, Gottlieb '379 teaches at most ""reduced inflammation is observed at HP-3 treated sites, due to the presence of suppressor activity" which is different from the claimed pharmaceutical composition.) That is the novel finding of the invention described in the instant application.

Hence, the examiner made improper use of the teachings of Gottlieb and of Chibret, resulting in improper assumptions and conclusions.

Withdrawal of the rejection is respectfully requested.

2. The examiner's inherency reasoning is not proper.

The examiner argued that the limitations of claim 1: "associated with the Metabolic Syndrome", claim 12: wherein said patient has at least one component of the Metabolic Syndrome" and claims 13, 15, 16: "wherein the symptom is a proinflammatory state" (i.e., a component of the metabolic syndrome) are inherent to contact dermatitis.

The examiner's inherency reasoning is not proper for the following reasons.

MPEP §2112 states that:

"The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)";

""To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999)

"Also, "[a]n invitation to investigate is not an inherent disclosure" where a prior art reference "discloses no more than a broad genus of potential applications of its discoveries." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367, 71 USPQ2d 1081, 1091 (Fed. Cir. 2004) (explaining that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category" but must be examined to see if a disclosure of the claimed species has been made or whether the prior art reference merely invites further experimentation to find the species.<"; and

"In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)"

Here, Chibret '936 discloses that "Contact dermatitis is an acute or chronic inflammation, often sharply demarcated, produced by substances in contact with the skin." As admitted by Chibret '936, contact dermatitis is not necessarily chronic inflammation. Contact dermatitis would only be considered chronic if the offending substance remained in contact with the skin for an extended period of time. Such inflammation may be seen, for example, under a watch or a ring containing certain metals which may cause a dry, red, scaly irritation which resolves when the contact with the skin is removed. This is quite different from a chronic systemic inflammation caused by a pathogen, excess production of cytokines, or inhalation of fine particulate foreign matter.

Since the examiner failed to provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art, the examiner's inherency reasoning is not proper.

In view of the above, all claims are deemed to be allowable and this application is believed to be in condition to be passed to issue. Reconsideration of the rejections and objections is requested. Should any questions remain unresolved, the Examiner is requested to telephone Applicant's attorney.

No fee is incurred by this Amendment.

Respectfully submitted,

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